DHEA and its transformation into androgens and estrogens in peripheral target tissues: intracrinology.

Abstract	A new understanding of the endocrinology of menopause is that women, at menopause, are not only lacking estrogens resulting from cessation of ovarian activity but have also been progressively deprived for a few years of androgens and some estrogens originating from adrenal DHEA and androstenedione (4-dione). In fact, serum DHEA decreases by about 60% between the maximal levels seen at 30 years of age to the age of menopause. This decreased secretion of DHEA and DHEA-S by the adrenals is responsible for a parallel decrease in androgen and estrogen formation in peripheral tissues by the steroidogenic enzymes specifically expressed in each cell type in individual target tissues. This new field of endocrinology, called intracrinology, describes the local synthesis of androgens and estrogens made locally in each cell of each peripheral tissue from the adrenal precursors DHEA and 4-dione. These androgens and estrogens exert their action in the same cells where their synthesis takes place and they are released from these target cells only after being inactivated. To further understand the effect of DHEA in women, DHEA has been administered in postmenopausal women for 12 months. Such treatment resulted in increased bone formation and higher bone mineral density accompanied by elevated levels of osteocalcin, a marker of bone formation. Vaginal maturation was stimulated, while no effect was observed on the endometrium. Preclinical studies, on the other hand, have shown that, due to its predominant conversion into androgens, DHEA prevents the development and inhibits the growth of dimethylbenz(a)anthracene-induced mammary carcinoma in the rat, a model of breast cancer. DHEA also inhibits the growth of human breast cancer ZR-75-1 xenografts in nude mice. The inhibitory effect of DHEA on breast cancer is due to an androgenic effect of testosterone and dihydrotestosterone made locally from DHEA. When used as replacement therapy, DHEA is free of the potential risk of breast and uterine cancer, while it stimulates bone formation and vaginal maturation and decreases insulin resistance. The combination of DHEA with a fourth generation SERM, such as EM-652 (SCH 57068), a compound having pure and potent antiestrogenic activity in the mammary gland and endometrium, could provide major benefits for women at menopause (inhibition

	of bone loss and serum cholesterol levels) with the associated major advantages of preventing breast and uterine cancer. A widely used application of intracrinology is the treatment of prostate cancer where the testicles are blocked by an LHRH agonist while the androgens made locally in the prostate from DHEA are blocked by a pure antiandrogen. Such treatment, called combined androgen blockade, has led to the first demonstration of a prolongation of life in prostate cancer.
Authors	F Labrie, V Luu-The, C Labrie, J Simard (Affiliation: Oncology and Molecular Endocrinology Research Center, Laval University Medical Center (CHUL), Quebec, G1V 4G2, Canada. fernand.labrie at crchul.ulaval.ca)
Journal	Frontiers in neuroendocrinology (Front Neuroendocrinol) Vol. 22 Issue 3 Pg. 185-212 (Jul 2001) ISSN: 0091-3022 United States
PMID	11456468 (Publication Type: Journal Article, Review)
Copyright	
Chemical References	